Current Biology, Vol. 13, R961–R963, December 16, 2003, ©2003 Elsevier Science Ltd. All rights reserved. DOI 10.1016/j.cub.2003.11.043

Energy Balance: A New Role for PPARα

Dispatch

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The nuclear receptor PPARα has been implicated in lipid and glucose homeostasis, although high affinity endogenous ligands have been elusive. The lipid oleylethanolamide has now been shown to be a true natural ligand for PPARα, and to participate in the regulation of food intake and body weight.

The epidemic of obesity and its unfortunate sequelae — including, but not limited to, type 2 diabetes, cardiovascular disease and certain cancers — continues to grow. Fortunately, recent discoveries have inspired a veritable gold rush of scientific activity on energy balance in academic and industrial labs alike. As a consequence, we have learned more about the central and peripheral regulation of appetite, adiposity, energy expenditure and nutrient metabolism in the last decade than in the preceding 100 years. No area has drawn more attention than the control of food intake, a field that got a huge boost in 1994 with the discovery of the adipocyte-derived hormone leptin [1]. Following that seminal finding, a whole panoply of other endogenous peptides have been identified that also play important roles in regulating body weight, including the melanocortins, neuropeptide Y (NPY), ghrelin, melanin-concentrating hormone (MCH) and others [2,3].

An unusual fatty acid ethanolamide has recently been added to the list of molecules that affect food intake. This molecule, oleylethanolamide, has structural similarity to the endogenous cannabinoid anandamide [4]. Because cannabinoids can induce hunger — as is well known to marijuana smokers who get the 'munchies' — a group of researchers decided to test whether oleylethanolamide could also affect food intake in rodents. Interestingly, they found that oleylethanolamide suppresses food intake, an effect opposite to that of anandamide [5]. Subsequent experiments showed that oleylethanolamide does not interact with the cannabinoid receptor. These data indicated that fatty acid ethanolamides have a surprising range of functions in the control of appetite, and opened the door for the discovery of a new receptor involved in mediating this process.

Many factors that regulate food intake, such as leptin and ghrelin, operate by directly stimulating receptors within the hypothalamus. These hormones interact with receptors on specific neurons in the arcuate nucleus, a region known to control appetite and body weight [2,3]. If small doses of leptin are injected directly into the central nervous system, for example, the effect is identical to that observed when the protein is administered peripherally. Other compounds affect appetite through both central and peripheral mechanisms. Cholecystokinin, for example, is a peptide secreted by the proximal small intestine in response to the ingestion of food, from whence it can act by direct stimulation of receptors in either the brain or the peripheral nervous system, specifically the vagus nerve [6].

If the vagus nerve is cut or damaged by a drug such as capsaicin, cholecystokinin's ability to reduce food intake is reduced. Similar experiments have shown that peripheral afferent neurons are also important for the

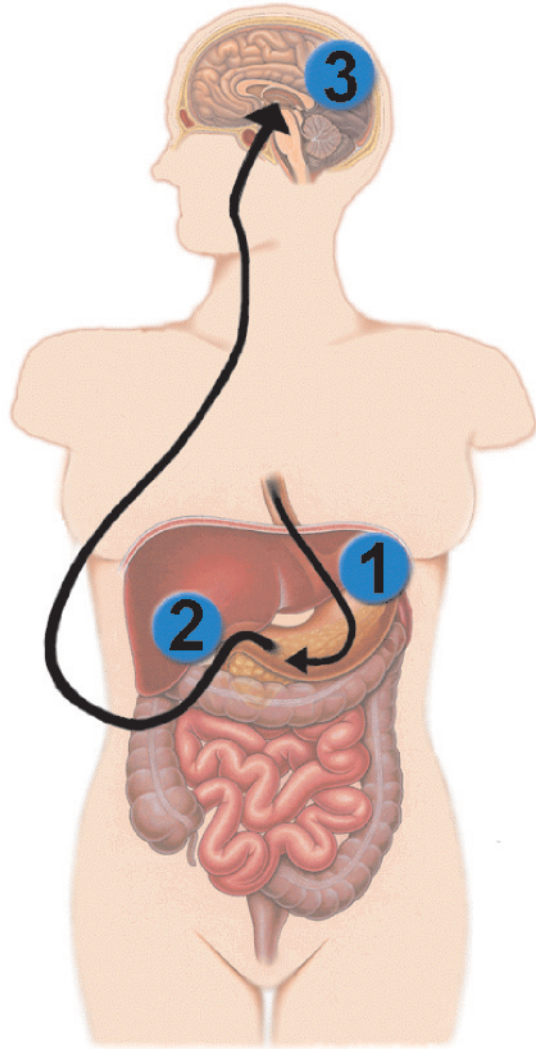

Figure 1. Role of oleylethanolamide in appetite regulation.

The ingestion of food (1) stimulates oleylethanolamide production in the proximal small intestine. Oleylethanolamide binds and activates its receptor, PPARα, probably in the epithelium (2), and PPARα-mediated transcriptional regulation of an as yet unidentified target gene(s) results in activation of peripheral afferents. These afferents terminate on appetite-regulating neurons in the brainstem and hypothalamus (3).

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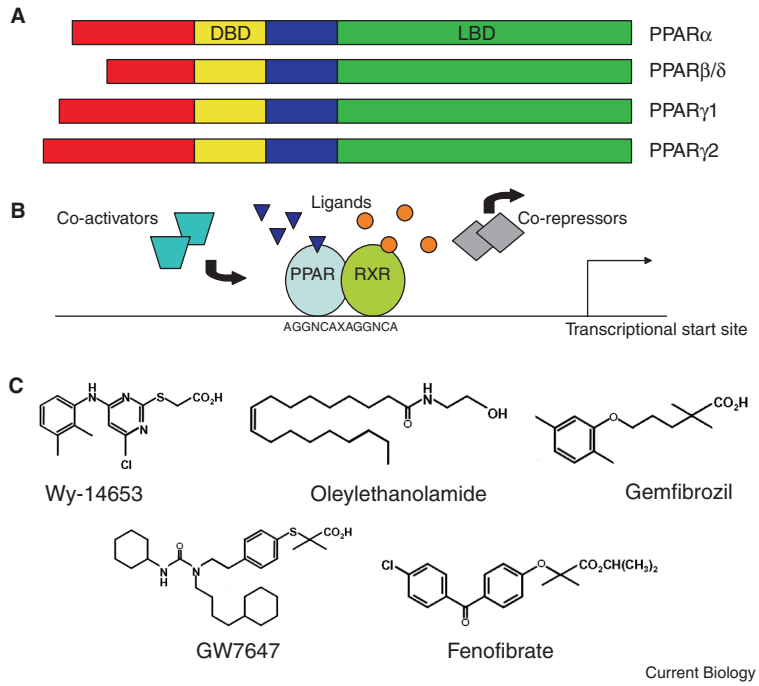

Figure 2. The PPARs.

(A) PPARα, δ, γ1 and γ2 all have the typical domain structure of a nuclear hormone receptor, with a central DNA-binding domain (DBD) and a carboxy-terminal ligand-binding domain (LBD). (B) PPARs act as obligate heterodimers with another nuclear hormone receptor called RXR. In the presence of ligands, co-activator proteins are recruited to supplant co-repressors and transcription is activated. (C) Known PPARα ligands, including fibrates in clinical use (fenofibrate, gemfibrozil), synthetic ligands (GW7647 and Wy-16453), and oleylethanolamide.

feeding effects of oleylethanolamide, but unlike cholecystokinin, oleylethanolamide is completely unable to reduce food intake when injected directly into the brain [5]. This suggests that oleylethanolamide's effects are fully mediated by peripheral activation of sensory nerves, presumably involving the vagus nerve (Figure 1). When oleylethanolamide is fed to rats, neuronal activity — measured indirectly as elevations in *c-fos* transcription — goes up in the paraventricular nucleus of the hypothalamus and the nucleus of the solitary tract of the brainstem, areas known to be associated with appetite control. Furthermore, oleylethanolamide levels have been shown to rise in the wall of the proximal small intestine upon feeding, and to fall with fasting [5], consistent with a role as an integrator of nutrient metabolism and food intake.

Perhaps the most obvious remaining question about oleylethanolamide has been the nature of its receptor. This question has now been answered by Fu *et al.* [7], who have identified the oleylethanolamide receptor as the peroxisome proliferator-activated receptor α (PPARα), an intriguing finding that unites two extremely hot areas of metabolic research, the control of food intake and the molecular biology of lipid and glucose homeostasis. As important as this finding is for the fields of obesity and metabolism, the therapeutic implications are likely to extend into seemingly unrelated areas such as the prevention and treatment of cancer and inflammatory diseases.

The PPARs are a subgroup of the large nuclear receptor superfamily [8]. Nuclear receptors are ligand-gated transcription factors that transduce physiological signals into gene expression changes in a bewildering array of biological activities, including organogenesis, cellular differentiation, reproduction, growth, bone mineralization and a plethora of other activities. The three PPAR genes in the human genome encode three basic protein isoforms, PPARα, PPARδ (sometimes called PPARβ) and PPARγ (Figure 2). An enormous body of work on PPARs over the last decade or so has revealed an extraordinary amount about their biology, and there are important drugs on the market specifically targeting their actions on lipid (PPARα) and glucose levels (PPARγ).

PPARα has been implicated in variety of metabolic processes, although notably not in the regulation of food intake. It is expressed in a variety of tissues, but most prominently in liver, heart, kidney, muscle and brown adipose tissue [9]. It is involved in up-regulating genes that affect many of the pathways operating in the fasting state, such as gluconeogenesis, ketogenesis and fatty acid uptake and oxidation. In concordance with this, PPARα null mice appear normal on a chow diet, but when fasted they become hypoglycemic, hypertriglyceridemic and hypoketonemic, with excess lipid stores in liver and other tissues [10,11]. Interestingly, PPARα null mice exhibit a non-significant decrease in food intake, an effect either neutral or in opposition to that predicted by the oleylethanolamide data [12].

Endogenous high-affinity ligands have not previously been identified for any PPAR isoform. Despite this, several synthetic ligands of PPARα were discovered empirically, and have been used clinically to reduce plasma lipid levels. These agents, collectively known as fibrates, have been shown to reduce body weight in obese rodent models, but until recently the effect had not been linked to reduced food intake [12]. Fu *et al.* [7] have now reported that oleylethanolamide binds to the ligand-binding domain of PPARα with an affinity in the mid-nanomolar range, consistent with the measured endogenous levels of oleylethanolamide inside the cells of the small intestine. This effect was specific for PPARα, as PPARδ and PPARγ showed little or no

response to oleylethanolamide. Additionally, other PPARα agonists were able to mimic the effects of oleylethanolamide, even though they exhibit little structural similarity (Figure 2C). Oleylethanolamide was also able to elicit 'traditional' effects of PPARα agonists, such as reducing triglyceride and cholesterol levels in obese rats. Most importantly, the effects of oleylethanolamide on body weight and food intake could not be elicited in PPARα null mice. Taken together, these data make a compelling case that oleylethanolamide is an endogenous ligand of PPARα, and that the appetite suppressant effects of oleylethanolamide are mediated by this interaction.

Many important questions remain, however. In which cells of the intestine is oleylethanolamide generated? A likely source would be the gut epithelium, the first cells to come into contact with nutrients in the lumen, and which are known to express PPARα [9]. It is possible, of course, that oleylethanolamide acts as a paracrine agent that enters nerve terminals in the intestinal wall, but then the signal would have to be transported in retrograde fashion for the length of the vagus nerve to the cell bodies in the nodose ganglia near the brainstem in order to reach PPARα in the cell nucleus. What are the targets of oleylethanolamide in the periphery that mediate the appetite suppressant effects? Fu *et al.* [7] suggest the nitric oxide synthetase iNOS as one possible target, and while this remains speculative, nitric oxide is known to modulate vagal nerve activity [13,14]. Which nutrients induce oleylethanolamide formation, and through what mechanism? Is oleylethanolamide the only high-affinity endogenous ligand for PPARα, or are there other ligands in other tissues or physiological contexts? Can novel synthetic PPARα ligands be developed that exert clinically significant appetite suppression?

Providing answers to these questions will keep researchers busy for a while, but ultimately the discovery of oleylethanolamide as a *bona fide* PPAR ligand is sure to spur the already intense race to discover other endogenous PPAR ligands. PPARγ in particular has been shown to have potent antidiabetic effects, and synthetic ligands are marketed for just that purpose. PPARγ also has anti-neoplastic and anti-inflammatory effects [15], and the discovery of novel chemicals that mediate these processes *in vivo* would be of enormous basic and therapeutic interest.

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